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(54) Title: PHARMACEUTICAL COMPOSITIONS

(57) Abstract: An extended release co mposit ion is disclosed which comprises the active compound pramipexole and provides a selected release profile. Preferably, the composition does not exhibit a lag phase of more than 1 hour. The composition is for suitable for oral administration. The invention also provides a method for achieving a 5 selected release profile, optionally by combining an extended release dose fraction and an immediate release dose fraction.

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Pharmaceutical compositions

FIELD OF THE INVENTION

The present invention is related to pharmaceutical compositions for oral administration. More specifically, the compositions are useful for the continuous therapy of diseases and conditions such as Parkinson's disease. The invention is also related to compositions useful for the administration of dopamine receptor agonists such as pramipexole. In a further aspect, the invention is related to methods of making compositions having selected release profiles.

BACKGROUND OF THE INVENTION

Oral drug delivery is commonly believed to be one of the most convenient methods in pharmacotherapy. In contrast to parenteral delivery, it is not invasive, and thus not associated with pain, discomfort, the risk of infections, or the need for assistance by a trained person. Oral delivery is usually very tolerable and reliable, provided the drug substance is orally bioavailable. As opposed to other non-invasive routes of drug administration, such as transdermal or pulmonary therapy, oral dosing is quick, convenient, and cost-effective.

It is known that patient compliance with oral dosing regimens is potentially high when the administration frequency is low. For example, three prescribed dosings a day are less often complied with than a regimen of only two or even only one administration per day.

Drug substances which do not have a plasma half life which is sufficiently long to allow a convenient dosing regimen, such as once a day, can be tried to be formulated as extended release formulations which provide the active ingredient to the organism over a prolonged period of time, and thus mimic two or more administrations of immediate

release formulations given at certain time intervals. However, this is only possible if the respective drug substance is stable, well absorbed along the gastrointestinal tract, and has a sufficiently large therapeutic window to allow for some increased degree of fluctuation in plasma concentrations which may occur during less frequent dosing. If the therapeutic window of the drug substance is relatively small, it may be challenging to develop an extended release formulation which is reliably effective and tolerable for large patient populations, regardless of individual physiological variability with regard to gastrointestinal pH ranges, the presence or absence of nutrients, gastrointestinal transit patterns and the motor activity of the stomach wall.

Parkinson's disease is an idiopathic, slowly progressive, degenerative CNS disorder characterized by slow and reduced movement, muscle rigidity, resting tremor, and postural instability. It is the fourth most common neurodegenerative disease of the elderly and affects about 1% of those of at least 65 years and 0.4% of those of more than 40 years. The mean age of onset is about 57 years. Occasionally, it may begin in childhood or adolescence, in which case it is referred to as juvenile parkinsonism.

Patients suffering from Parkinson's disease are typically candidates for long-term pharmacotherapy. Such patients would clearly profit from safe and convenient dosing regimens, which would result in a high degree of compliance, effectiveness and tolerability of their therapy.

Pramipexole is a dopamine agonist currently in some countries approved for the treatment of the signs and symptoms of idiopathic Parkinson's disease and RLS. It is structurally different from older dopaminergic drugs, such as the ergot-derived compounds, e.g. bromocriptine or pergolide. It is also pharmacologically unique in that it is a full agonist and has a high selectivity for the dopamine D2 family of dopamine receptors.

Pramipexole is available in the form of immediate release (IR) tablets which contain pramipexole dihydrochloride monohydrate. For treating Parkinson's disease tablets have to be taken 3 times a day. A typical immediate release tablet, which in Germany is known under the trade name Sifrol®, comprises as inactive ingredients mannitol, corn starch, colloidal silicon dioxide, povidone, and magnesium stearate and

0.125 mg, 0.25 mg, 0.5 mg or 1.0 mg of pramipexole dihydrochloride monohydrate. This tablet also is the reference, whenever it is referred to an immediate release tablet and not otherwise specified in the context of this description.

While there is a clear need for an effective and tolerable extended release formulation of pramipexole no product has been made commercially available.

WO 2004/010997 describes a sustained-release pharmaceutical composition in a form of an orally deliverable tablet comprising a water-soluble salt of pramipexole, dispersed in a matrix comprising a hydrophilic polymer and a starch having a tensile strength of at least about 0.15 kN cm^{-2}, at a solid fraction representative of the tablet. The disclosure thereof is concentrated to provide a composition with sufficient hardness yield during a high-speed tableting operation, in particular to resist erosion during application of a coating layer. According to a preferred embodiment it is provided a pharmaceutical composition in a form of an orally deliverable tablet having a core comprising pramipexole dihydrochloride monohydrate in an amount of about 0.375, 0.75, 1.5, 3 or 4.5 mg, dispersed in a matrix comprising (a) HPMC type 2208 in an amount of about 35% to about 50% by weight of the tablet and (b) a pregelatinised starch at a solid fraction of 0.8, in an amount of about 45% to about 65% by weight of the tablet; said core being substantially enclosed in a coating that constitutes about 2% to about 7% of the weight of the tablet, said coating comprising an ethylcellulose-based hydrophobic or water-insoluble component and an HPMC-based pore-forming component in an amount of about 10% to about 40% by weight of the ethylcellulose-based component.

Furthermore, WO 2004/010999 discloses an orally deliverable pharmaceutical composition comprising a therapeutically effective amount of pramipexole or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable excipient, said composition exhibiting at least one of (a) an in vitro release profile wherein on average no more than about 20% of the pramipexole is dissolved within 2 hours after placement of the composition in a standard dissolution test; and (b) an in vivo pramipexole absorption profile following single dose oral administration to healthy

adult humans wherein the time to reach a mean of 20% absorption is greater than about 2 hours and/or the time to reach a mean of 40% absorption is greater than about 4 hours.

In spite of the fact that certain pramipexole-containing extended release compositions have been provided in prior art, there remains a need for further compositions and methods of making such compositions which allow the precise predetermination and control of the release profile of pramipexole. There also remains a need for extended release compositions of pramipexole which can be manufactured cost-effectively, which are suitable for various types of patients, and which can overcome the limitations of the known compositions.

SUMMARY OF THE INVENTION

In a first aspect, the invention provides a method for making a pharmaceutical extended release composition comprising a therapeutically effective dose of pramipexole or one of its pharmaceutically acceptable salts, derivatives, solvates, and isomers. The method comprises the steps of:

(a) defining a desirable release profile;

(b) selecting a total dose of pramipexole to be incorporated in the composition;

(c) selecting a first fraction of said total dose to be incorporated in the composition in extended release form, and selecting a second fraction of said total dose to be incorporated in the composition in immediate release form; and

(d) combining said first and said second fractions into a composition exhibiting the release profile defined in step (a).

The method allows the use of an extended release formulation of pramipexole even if it does not fully match the desired release profile. In particular, the desired release profile may not include a significant lag phase, whereas an extended release formulation may exhibit such lag phase. In this case, the method provides that the extended release formulation is combined with an immediate release formulation so as to form a composition which exhibits extended release without lag phase. On the other hand, if an extended release form of pramipexole matches the desired or predefined

release profile, the immediate release dose fraction to be incorporated may be selected to be 0 % of the total dose.

In a second principal aspect, the invention provides a pharmaceutical composition comprising a therapeutically effective dose of an active compound selected from pramipexole and its pharmaceutically acceptable salts, derivatives, solvates, and isomers, wherein a first fraction of said dose is incorporated in the composition in extended release form and a second fraction of the dose is incorporated in immediate release form. Preferably, the first dose fraction comprises from about 50 to 100 wt.-% (preferably 50 to 99.5 wt.-%) of the total incorporated dose of pramipexole, and the second dose fraction comprises from about 0 to 50 wt.-% (preferably 0.5 to 50 wt.-%) of the total dose.

In a third principal aspect, the invention provides a range of novel extended release formulations of pramipexole which may be used as such in the manufacture of medicaments, or which may be used in combination with immediate release formulations of pramipexole.

DETAILED DESCRIPTION OF THE INVENTION

The invention provides, inter alia, a method for making a pharmaceutical extended release composition comprising a therapeutically effective dose of pramipexole or one of its pharmaceutically acceptable salts, derivatives, solvates, and isomers. The method comprises the steps of: (a) defining a desirable release profile; (b) selecting a total dose of pramipexole to be incorporated in the composition; (c) selecting a first fraction of said total dose to be incorporated in the composition in extended release form, and selecting a second fraction of said total dose to be incorporated in the composition in immediate release form; and (d) combining said first and said second fractions into a composition exhibiting the release profile defined in step (a).

A preferred form of pramipexole which is comprised in the composition is a water soluble salt or hydrate thereof, in particular pramipexole dihydrochloride monohydrate. However, other water soluble forms, or even poorly water soluble forms of pramipexole may also be selected as active ingredient in certain cases which will be pointed out herein-below. As used herein, the term pramipexole is understood as covering all forms

of Pramipexole, the free base as well as pharmaceutically acceptable salts and solvates thereof, including pramipexole dihydrochloride monohydrate.

The method is aimed at providing an oral extended release composition of pramipexole which is suitable for a wide range of therapeutic applications and patient groups. In particular, the method is directed to obtaining a composition which exhibits a defined, or preselected release profile. The preferred release profile comprises a period of release of at least 4 hours, such as from about 4 to about 24 hours. More preferably, the duration of pramipexole release having therapeutic effect is at least 6 hours, or at least 8 hours, or from about 12 to about 24 hours.

Another preferred feature of the release profile is that it is relatively smooth, without abrupt changes in release rate, such as dose dumping effects. Moreover, it is preferred that the release profile does not exhibit a pronounced lag phase, such as a lag phase of more than 60 minutes, and more preferably there is no lag phase of more than about 30 minutes. Optionally, a lag phase of 15 or more minutes is substantially absent. A lag phase is understood as an initial period of no or negligible drug release, such as a release of less than about 5 % of the dose comprised in the composition, at a rate substantially below the average release rate of the profile. Lag phases are sometimes present in extended release formulations, but they may not be desirable as they can lead, in continuous therapy, to fluctuations of the plasma levels of pramipexole.

The total dose of pramipexole which is selected for incorporation per dosage unit may depend on factors such as the therapeutic needs of the patient to be treated, the condition of the patient, the duration of drug release according to the predefined release profile, and the intended administration interval. Preferably, the method is applied for making a composition which is suitable for once daily or twice daily administration, particularly for once daily administration. A suitable total dose is in the range from about 0.375 to about 4.5 mg pramipexole per dose unit, calculated as pramipexole dihydrochloride monohydrate. More preferably, the composition comprises from about 0.5 mg to about 1.5 mg of pramipexole. Presently most preferred is a dose of about 0.75 mg.

The method further comprises the step of selecting a first fraction of said total dose to be incorporated in the composition in extended release form, and selecting a

second fraction of said total dose to be incorporated in the composition in immediate release form. This step may be carried out in consideration of particular features of the predefined release profile which should be achieved. The selection may take into consideration any known or anticipated deficiencies in release behaviour of the extended release formulation which is to be used for the preparation of the composition. For example, if the composition is intended to exhibit a somewhat faster initial period of drug release, a certain percentage, such as up to about 50 %, of the dose may be selected to be in immediate release form so that the desired type of release curve is obtained. Or, for another example, it may be known or anticipated that a certain extended release formulation which is to be incorporated exhibits an undesired release behaviour, such as a pronounced lag time. Selecting a fraction of the pramipexole to be incorporated in immediate release form may compensate this defect and effect that the overall release profile of the composition is smooth and without lag phase.

On the other hand, if the extended release formulation intended to be incorporated in the composition exhibits an acceptable release profile, it may be appropriate to select the extended release fraction to be 100 % of the pramipexole dose and, accordingly, the dose fraction which is in immediate release form to be 0 (zero) %. In fact, one of the preferred embodiments is a method in which the immediate release dose fraction is selected to be 0 %. In other embodiments, the immediate release dose fraction is up to 50 % of the dose, such as about 10 %, or from about 20 to 50 %, or from about 25 to about 33.3 %. The presently preferred selections for the extended release dose fraction are, accordingly, about 100 %, or about 90 %, or from about 50 to about 80 %, or from about 66.7 to 75 % of the total dose, respectively.

As used herein, an immediate release form means a formulation which, by itself, releases its incorporated pramipexole completely (i.e. at least 95 % of the incorporated amount) within not more than about one hour when tested in vitro according to a standard dissolution test according to USP 28 (United States Pharmacopoeia). In contrast, an extended release form means a formulation which, by itself, releases its incorporated pramipexole completely (i.e. at least 95 %) over a period of at least about 4 hours when tested in vitro.

According to a second principal aspect, the invention provides a pharmaceutical composition comprising a therapeutically effective dose of an active compound selected

from pramipexole and its pharmaceutically acceptable salts, derivatives, solvates, and isomers, wherein a first fraction of said dose is incorporated in the composition in extended release form and a second fraction of the dose is incorporated in immediate release form. Preferably, the first dose fraction comprises from about 50 to 100 wt.-% of the total incorporated dose of pramipexole, and the second dose fraction comprises from about 0 to 50 wt.-% of the total dose.

Various dosage form designs can be used to accommodate both an extended release fraction and an immediate release fraction of the dose of the pramipexole. Particularly useful designs are tablets and hard capsules. A tablet is defined herein as a solid unit prepared by the compaction of a powder, granules, or pellets. Subclasses of tablets include simple tablets, dispersible tablets, sugar-coated tablets, film-coated tablets, press-coated tablets, osmotic tablets, layer tablets, and tablets with special geometrical design. Hard capsules are usually defined as units comprising a two-piece capsule shell encapsulating a powder, granules, pellets, microcapsules, a coherent liquid, solid or semi-solid matrix, or small tablets. Optionally, a hard capsule may be coated with a polymeric film-coating. Both tablets and capsules can be designed either as single-unit dosage forms or multiple-unit dosage forms, the difference being that the overall release profile of a multiple-unit dosage form is predominantly determined by a number of similar functional subunits contained in the dosage form, such as pellets.

If the dose fraction which is in extended release form is 100% of the dose, i.e. if no immediate release fraction is present, an even larger range of dosage form designs is useful for practising the invention. While tablets and hard capsules are also in this case very useful and preferred designs, it is also possible to formulate the composition into a soft capsule or monolithic extrudate. Soft capsules are capsules having a hydrogel shell, typically based on gelatin, a plasticiser such as glycerol, and water, and which comprise an encapsulated material which is most often liquid, but can also be semi-solid or even solid material, such as a solidified melt.

Extrudates are herein understood as solid single units which have been shaped by forcing a plastically deformable material through an orifice. For shaping an extrudate, a composition may be deformed under pressure, heat or both. Thus, the term "extrudate", as used herein, also includes solid forms prepared by injection molding.

If the immediate release fraction of pramipexole is different from 0% and the dosage form design of a tablet is selected, the tablet may be designed to contain multiple functional units which comprise the extended release dose fraction. For example, such tablets may be composed of extended release pellets and immediate release pellets, or of extended release pellets which have been admixed with a powder or granule component comprising the immediate release dose fraction, and which mixture has been compressed into tablets. Upon contact with a dissolution medium, such tablets disintegrate rapidly and discharge their functional subunits, i.e. the extended release pellets, which are themselves resistant to disintegration for at least a substantial part of the intended period of drug release.

One aspect of the present invention refers to pharmaceutical units comprising extended release pellets and microparticles. Such pellets and microparticles can be filled into hard capsules to provide an extended release formulation or incorporated into compressed tablets without impairing their release-related functionality. These methods include, for example, the use of low compression forces in combination with the incorporation of a highly effective dry binding agent, or the incorporation of soft "cushioning" particles in the tableting mixture to preserve the integrity of the extended release pellets or microcapsules during compression. If the extended release units have polymeric coatings which provide control over the release of the active compounds, it is useful to plasticise these coatings to a higher degree than for other dosage forms in order to render them substantially deformable, which may prevent their rupture during compression leading to a loss of functionality. Suitable plasticisers and concentrations thereof which would lead to a flexible coating are generally known to the expert in the field, e.g. from Dashevsky et al., Compression of pellets coated with various aqueous polymer dispersions (Int. J. Pharm. 279, 19-26, 2004).

According to the invention among the particularly preferred cushioning beads are beads with a diameter of 0.5 to 2 mm and a content of at least about 30 wt.-% of a cushioning component. This cushioning component is preferably a microcrystalline hydrocarbon wax or a natural wax useful for the compression of tablets from mechanically sensitive extended release units.

The pellets, beads or microcapsules themselves which comprise the dose fraction of pramipexole that is in extended release form can be prepared by a variety of methods,

using various types of excipients and processing equipment. Some particularly useful pellet, bead or microcapsule compositions according to the invention and some preferred methods of making such units will be discussed herein-below in the context of hard capsules, which may also be filled with such units in order to obtain the composition of the present invention.

The present invention does not only comprise multiple-unit configurations but also a tablet comprising an immediate release and an extended release fraction of pramipexole in form of a single-unit dosage form which comprises the extended release portion in one compartment and the immediate release fraction in another, spatially separated compartment. Such embodiment comprises a layer tablet as well as a press-coated tablet. Layer tablets are tablets having two or more compressed layers. Typically, there is a difference in composition and function between at least two of the layers of a layer tablet. A press-coated tablet, also referred to as dry-coated or compression-coated tablet, is a unit formed by the incorporation of a smaller tablet, or core tablet, into a larger tablet. As used herein, press-coated tablets also include tablet designs in which the core tablet is not fully, but only partially covered with the press-coating, resulting in special geometric configurations such as the so-called bull's-eye tablets.

In any of these tablets, at least two spatially distinct compartments are present which may incorporate the extended release dose fraction and the immediate release dose fraction of pramipexole, respectively. For example, a two-layer tablet may comprise one layer which disintegrates rapidly when exposed to an aqueous medium such as (simulated) gastric or intestinal fluid and release its incorporated active ingredient rapidly, and a second layer which does not disintegrate rapidly, and which is composed like an extended-release matrix tablet.

One of the particularly preferred embodiments according to the present invention comprises elements of the so-called Geomatrix® technology. The tablet according to the invention comprises a swellable, hydrogel-forming layer containing Pramipexole, preferably in for the dihydrochloride monohydrate, or at least that portion of the active ingredient which is to be released slowly. This matrix layer comprises either a combination of a hydrogel-forming polymer and a polymer which swells strongly in water, or a polymer which both gels and swells. Polymers having a high degree of swelling include, for example, cross-linked sodium carboxymethylcellulose, cross-

linked hydroxypropylcellulose, high-molecular weight hydroxypropyl methylcellulose, carboxymethylamide, potassium methacrylate-divinylbenzene copolymer, polymethylmethacrylate, cross-linked polyvinylpyrrolidone, high-molecular weight polyvinylalcohols etc. Gellable polymers include methylcellulose, carboxymethylcellulose, low-molecular weight hydroxypropyl methylcellulose, low-molecular weight polyvinylalcohols, polyoxyethylene glycols, and non-cross linked polyvinylpyrrolidone. Polymers which possess both swelling and gelling properties include medium-viscosity hydroxypropyl methylcellulose and medium-viscosity polyvinyl alcohol.

From this type of layer tablet, pramipexole is released by diffusion through the hydrogel and/or by the erosion of the gel. Additionally, the tablet has one or more insoluble or slowly erodible barrier layers adjacent to the matrix layer which control the surface area of the matrix which is available or effective for drug release. In a further embodiment an immediate release dose fraction is incorporated in an outer layer of the tablet.

In an advanced embodiment of this aspect of the invention a layer tablet is designed. The swellable matrix layer comprises from about 0.375 mg to about 4.5 mg of pramipexole, calculated as pramipexole dihydrochloride monohydrate, and more preferably from about 0.375 mg to about 1.5 mg. Particularly preferred is a content of about 0.75 mg. Preferably, the tablet comprises one or two drug-free barrier layers which comprise an insoluble polymer, such as ethylcellulose, cellulose acetate or cellulose acetate butyrate.

It is also preferred that the tablet diameter is from about 6 to about 12 mm, or from 7 to 11 mm, and that the total thickness of the tablet in the dry state is from 3 to about 7 mm. According to another embodiment, at least about 40 %, and preferably at least about 50 %, of the thickness of the layer tablet in the dry state is accounted for by the swellable matrix layer. Optionally, the ratio of the tablet diameter to the tablet thickness is from about 0.7 : 1 to about 1 : 1.5.

According to a further embodiment, the tablet is designed to have one swellable matrix layer comprising at least 50 % of the dose of the active ingredient in extended release form, one drug-free outer barrier layer which is insoluble or slowly erodible in

an aqueous medium, and one further outer layer which comprises from about 20 % to about 50 % of the dose in immediate release form.

In another approach to making layer tablets according to the invention a core layer is covered by one or two erodible layers which exhibit a thickness characterised by a gradient. The core layer is resistant to disintegration and releases its incorporated active ingredient primarily by diffusion. To maintain the rate of drug release over the entire release profile, the covering layers erode continuously, which causes a continuous increase in surface area of the matrix layer.

The layer tablet is characterised by an asymmetrical covering layers regardless of whether the first fraction of the dose of pramipexole is zero percent or not. If the whole dose of the composition is in extended release form, it is incorporated within the core layer of the tablet. Optionally, an immediate release dose fraction can be incorporated within at least one erodible covering layer.

The matrix-forming excipient of the non-disintegrating core layer is preferably a wax, such as carnauba wax, a lipid, such as hydrogenated castor oil, or an insoluble polymer, such as cellulose acetate butyrate or polyethylene oxide.

With respect to the core layer of such tablet, it is preferred that it comprises from about 0.375 mg to about 4.5 mg of the active compound, calculated as pramipexole dihydrochloride monohydrate, and more preferably from about 0.375 mg to about 1.5 mg. Particularly preferred is a content of about 0.75 mg.

The tablet diameter should preferably be selected in the region from about 8 to about 13 mm, and the total tablet thickness in the region from about 4 to about 8 mm in the dry state. The relatively larger diameter of this type of layer tablet is useful for allowing the thickness gradients of the covering layers to precisely control the release of the active ingredient from the core layer. Preferably, the tablet comprises one core layer and two erodible outer layers, whether an immediate release dose fraction is present or not.

An alternative embodiment according to the present invention refers to a tablet design with at least two spatially separated compartments. Preferred are press-coated tablets. In this case the outer coating of the tablet preferably comprises the immediate

release dose fraction of pramipexole, and the core of the tablet comprises the dose fraction which is in extended release form. In fact, a press-coated tablet has been found particularly useful for those embodiments in which the immediate release fraction of the dose is substantially different from 0%.

The coating is preferably formulated as a tablet composition which disintegrates rapidly in gastrointestinal fluid. In particular, the coating may comprise one or more disintegrants which are selected in type and quantity to achieve a disintegration time of the coating layer of less than about 30 minutes, as measured in vitro using a disintegration tester which conforms with the USP 28 basket-rack apparatus assembly, using water as the immersion fluid. More preferably, the disintegration time of the coating layer is less than about 15 minutes, or less than about 10 minutes, respectively.

Appropriate disintegrants to achieve such disintegration times include alginic acid, carboxymethylcellulose, low-substituted hydroxypropyl cellulose, microcrystalline cellulose, powdered cellulose, colloidal silicon dioxide, croscarmellose sodium, crospovidone, magnesium aluminium silicate, methylcellulose, povidone, sodium alginate, sodium starch glycolate, starch etc.

The core of the press-coated tablet is preferably formulated as an extended release matrix tablet, either based on one or more hydrophilic or lipophilic matrix-forming excipients. Methods and compositions to design and manufacture such extended release matrix tablets are generally known to a person trained in the field of pharmaceutics. Some of the preferred selections with regard to appropriate excipients will be discussed in more detail herein-below.

In embodiments with no immediate release dose fraction of pramipexole the design of a press-coated tablet can be applied as well for maintaining a certain desired release rate throughout the period of drug release. In this case, the extended release dose fraction can also be incorporated in the outer coating layer of the tablet, which must be formulated to be non-disintegrating, at least over a period of several hours. In fact, in this case the coating can be formulated as a hydrophilic or lipophilic extended release matrix which erodes slowly and provides drug release by diffusion and/or erosion over a period of about 4 to 20 hours. Near the end of the release period, the rate of release from a matrix typically decreases, which is an effect of several factors, one of which is the

depletion of the matrix of active ingredient, resulting in a continuously smaller concentration gradient of the drug from the inside to the outside of the matrix. The concentration gradient is the driving force for drug release by diffusion; therefore, a smaller concentration gradient near the end of the duration of drug release is associated with a decreased rate of release.

To maintain a certain desired rate of release until the end of the intended release period, the core tablet according to one aspect of the present invention may be formulated as an immediate release composition, so that when the outer extended release matrix is close to depletion and has undergone extensive erosion, the core formulation can provide another pulse of drug release. If the immediate release dose fraction incorporated within the tablet core is relatively large, such as about 20 to 50% of the total incorporated dose, the overall release rate of the coated tablet may even increase at the time the tablet core becomes exposed to the dissolution medium.

One embodiment of this aspect of the present invention refers to a dry-coated tablet having a core comprising a water-soluble active agent and a waxy material and a coating comprising the water-soluble active agent and a hydrophilic polymer, wherein the coating composition is press-coated onto the core composition. The core is typically formulated as a lipophilic matrix with its individually tailored drug release profile, whereas the coating is typically also an extended release matrix, but based on a gellable and water-swellable polymer which may release the drug at a different rate profile. The hydrophilic polymer is preferably selected from hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPC), hydroxypropyl methylcellulose (HPMC), hydroxypropyl ethylcellulose (HPEC), hydroxypropyl propylcellulose (HPPC), hydroxypropyl butylcellulose (HPBC), and mixtures thereof. The waxy matrix-forming agent of the core may be carnauba wax, tribehenin, a fatty alcohol, such as lauryl alcohol, myristyl alcohol, stearyl alcohol, palmityl alcohol, a fatty acid, such as lauric acid, myristic acid, stearic acid, palmitic acid, polyethylene, castor wax, medium to long chain fatty acid triglycerides, beeswax, or mixtures of any of these. Optionally, further excipients and characteristics may be used to make the tablet, such as the excipients disclosed in WO 2004/108082, which is fully incorporated herein.

A further embodiment of the invention is directed to unit comprising at least two distinct compartments to achieve a desired release profile. The dosage units are

preferably shaped by injection molding or melt extrusion, even though the appearance of the product may be similar to that of a tablet. It has been found that in this way a composition can be formulated which releases pramipexole according to a predetermined, extended release profile over a period of about 4 to 24 hours, in particular over about 8 to about 20 hours.

According to this embodiment, at least one pramipexole-containing extended release matrix compartment is present in the dosage unit. The matrix is surface-erodible, and pramipexole is released primarily by the erosion of the matrix surface. The composition of the matrix is preferably based on an at least partially crystalline polymer, such as a polyglycol. It is preferred according to the invention that a homo- or copolymer of ethylene glycol, or ethylene oxide, is used. Particularly suitable polyethylene oxides for formulating pramipexole have a molecular weight in the range from about 10,000 to about 500,000, especially from about 35,000 to about 300,000. Alternatively or additionally, a block copolymer of ethylene oxide and propylene oxide may be used, preferably having a polyethylene oxide content of at least about 65 % and a molecular weight of at least about 5,000. The at least partially crystalline polymer matrix should have a melting point which is clearly above the body temperature, such as in the range from about 40 to about 80 °C.

Optionally, the matrix component may further comprise one or more surfactants. At least one of the surfactants should comprise a hydrophilic moiety which is compatible with the at least partially crystalline polymer. For example, a moiety which is compatible with the afore-mentioned polyethylene oxides and block copolymer of ethylene oxide and propylene oxide is a polyethylene glycol moiety. However, other hydrophilic moieties may also be compatible. Thus, surfactants comprising a polyethylene glycol moiety are particularly useful.

In another aspect, it is preferred that the surfactant comprises a lipophilic moiety which comprises a hydrocarbon chain of at least about 10 carbon atoms, such as a medium chain fatty acid or -alcohol residue, for example derived from palmitic or stearic acid. Moreover, the hydrophilic-lipophilic balance (HLB) of the surfactant is preferably in the range from about 5 to about 15. Optionally, the surfactant also comprises a sorbitan moiety. Among the preferred surfactants is polyethylene glycol monostearate, such as polyethylene glycol 400 monostearate.

The surface erodible matrix comprises up to about 85 wt.-% of the matrix-forming crystalline polymer, or of the mixture of the polymer and the surfactant(s). In other preferred embodiments, these matrix-forming constituents are incorporated at a content in the range from about 30 to about 75 wt.-%, such as from about 40 to about 70 wt.-%.

The second compartment present in this dosage form design is a coating which partially covers or surrounds the matrix. The coating layer may be bioerodible or insoluble, but if it is bioerodible it erodes at a slower rate than the matrix. The coating layer is substantially impermeable to the drug, so that drug release primarily occurs through the erosion of that part of the matrix surface which is not covered by the coating. Furthermore, the coating is designed so as to achieve that the part of the matrix surface area which is not covered remains substantially constant during drug release. For example, the matrix may be formed as an elliptic or circular cylinder, and the coating may be designed to cover the cylinder except for one or both of the flat ends.

The coating may also comprise a polymer, in particular a polymer which effects a relatively long period of resistance to dissolution, disintegration or erosion so that the coating continues to cover a part of the matrix until the predetermined release of pramipexole is completed. Optionally, the polymer is selected from cellulose derivatives, such as thermoplastic cellulose ethers or -esters, e.g. cellulose acetate, cellulose acetate butyrate, ethyl cellulose, optionally in combination with a hydrophilic, water-soluble cellulose derivative, such as a hydroxyalkyl cellulose, e.g. hydroxyethyl cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, and hydroxypropyl methylcellulose. Further optional polymeric constituents of the coating include polyamide, polyethylene, polyethylene terephthalate, polypropylene, polyurethane, polyvinyl acetate, polyvinyl chloride, silicone rubber, latex, polyhydroxybutyrate, polyhydroxyvalerate, teflon, polylactic acid or polyglycolic acid and copolymers thereof, copolymers such as ethylene vinyl acetate, styrene-butadiene-styrene and styrene isoprene-styrene. The coating may further comprise low molecular weight excipients, such as one or more fillers, plasticisers, pigments, etc.

In embodiments with an immediate release dose fraction of pramipexole, preferably a third compartment is present in the dosage unit which is rapidly erodible or fast disintegrating. This compartment may also be formulated as a thermoplastic mixture and shaped by melt extrusion or injection molding, or by a similar process

using heat. It may initially cover the part of the matrix surface which will, during the major portion of the release period, erode continuously and provide extended release of its incorporated dose fraction. This immediate release compartment may comprise from about 0 wt.-% (preferably from about 0.5 wt.-%) to about 50 wt.-% of the total incorporated dose of pramipexole. In the presently preferred embodiments, the dose fraction which is incorporated in immediate release form is either 0 wt.-% or from about 20 wt.-% to about 50 wt.-%, such as from about 25 wt.-% to about 33.3 wt.-% of the total incorporated pramipexole. If 0 wt.-% is selected, it is preferred that the dosage form prepared according to this embodiment comprises only an extended release matrix compartment and a coating, but no further compartment.

A further embodiment according to the current invention comprises an extended release matrix which is covered by a coating which is substantially impermeable to pramipexole. Appropriate coating materials include, for example, ethyl cellulose, cellulose acetate, cellulose acetate butyrate and certain methacrylic acid copolymers such as Eudragit RS and similar products. Typically, the coating has a higher thickness than extended release coatings of conventional tablets or pellets.

In one region of the core, a cylindrical plug is embedded near the surface, which plug may or may not be covered by the coating. The plug may be hollow or solid, and it is preferably composed of a swellable hydrogel-forming material, such as a mixture comprising a superdisintegrant like croscarmellose sodium, crospovidone, or sodium starch glycolate. The diameter of the plug is preferably selected from the range of about 4 to 9 mm, and in the case that the plug is hollow, the inner diameter is preferably from about 1 to about 4 mm. The plug may also be in the form of a bilayer tablet, in which one of the layers comprises an immediate release dose fraction of pramipexole, which is in this case preferably from about 20 to about 33.3 % of the total incorporated dose.

The matrix preferably is formulated as a slowly erodible composition, such as based on a polyethylene oxide-containing excipient mixture. It comprises a fraction of the pramipexole dose ranging from about 66.6% to about 100% of the total incorporated dose. It requires water in order to erode, which water may be taken up through the coating which is impermeable to the drug, but not to water.

The release of the drug from the matrix occurs through the passageway opened by the plug as it forms a hydrogel in the presence of water. The swelling of the plug may cause it to break through the coating. Thereafter, the rate of release is primarily determined by the size, geometry (whether hollow or not), and composition of the plug.

The immediate release dose fraction of pramipexole may also be incorporated in the dosage unit in form of an additional coating layer, which may be applied e.g. by compression coating.

The dosage unit may be prepared by generally known compression techniques and coating methods.

In some further embodiments, the composition of the invention is also designed as a unit coated with a coating which is permeable to water, but impermeable to pramipexole, and wherein the release of pramipexole occurs through one or more apertures in the coating. In contrast to the plug in the above described dosage form, the apertures in these drug delivery systems are generally very small, such as substantially below 1 mm in diameter.

In these embodiments, the release of pramipexole is driven by the pressure increase within the coating, which pressure may be osmotic pressure or the mechanical pressure exerted by a swelling hydrogel, or both. Above a certain pressure threshold, the system relaxes by expelling a small portion of its content, i.e. of an aqueous drug solution or suspension, through the orifice. After this, the pressure builds up again, until another small portion of the content is expelled, which cycle continuous until the reservoir is depleted. Because of the role of the osmotic pressure, this dosage form design is also referred to as osmotic tablet, osmotic system, or osmotic pump.

Osmotic dosage forms can be designed to achieve a substantially constant overall rate of pramipexole release by configuring the system to provide a relatively constant osmotic pressure and having suitable exit means to permit the dissolved or suspended pramipexole to be released at a rate that corresponds to the rate of fluid imbibed as a result of the relatively constant osmotic pressure. A significant advantage of osmotic systems is that their operation is pH-independent and thus continues at the osmotically-determined rate throughout an extended time period even as the dosage form transits the

gastrointestinal tract and encounters differing microenvironments having significantly different pH values.

Optionally, a very simple osmotic device comprising pramipexole in a mixture with excipients, optionally including osmotically active components, within the same compartment can be designed. According to a more sophisticated design, the osmotic device comprises two component layers within the compartment formed by the semipermeable wall. One component layer comprises pramipexole in a mixture with excipients, optionally including osmotically active components, that will form a deliverable drug formulation within the compartment. A second component layer comprises at least one osmotically active excipient, but does not contain pramipexole. The osmotically active excipient in the second component layer typically comprises an osmotically active polymer which has a relatively large molecular weight and swells as fluid is imbibed, so that release of these components through the drug formulation exit means does not occur. If a fluid is imbibed, the polymer swells and pushes against the pramipexole formulation of the first component layer to thereby effect release of pramipexole at a substantially constant rate.

According to this embodiment, the wall or coating of the dosage unit is preferably prepared from a water-insoluble cellulose derivative, in particular ethyl cellulose, cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose acetate butyrate, cellulose diacetate and cellulose triacetate. The coating thickness is adapted to control the rate of water uptake into the inner reservoir; since the surface area remains substantially constant throughout the drug release period, it is primarily the thickness of the coating which determines the rate at which the internal pressure of the system increases.

The swellable hydrogel-forming component of the push layer preferably comprises a polymer capable of swelling at least to a twofold increase in volume. Useful polymers for this purpose include, for example, polyhydroxyalkyl methacrylates such as polyhydroxymethyl methacrylate, polyhydroxyethyl methacrylate, polyhydroxypropyl methacrylate, polyvinylpyrrolidone, crosslinked starch, crosslinked amylose, hydroxypropyl methylcellulose, crospovidone, croscarmellose, anionic and cationic hydrogels, polyelectrolyte complexes, polyvinyl alcohol having a low acetate residual and cross-linked with glyoxal, formaldehyde, or glutaraldehyde, methyl

cellulose cross-linked with dialdehyde, a mixture of cross-linked agar and carboxymethyl cellulose, a water insoluble, water-swellable copolymer produced by forming a dispersion of finely divided copolymer of maleic anhydride with styrene, ethylene, propylene, butylene, or isobutylene cross-linked with a polyunsaturated cross-linking agent per mole of maleic anhydride in the copolymer, water-swellable polymers of N-vinyl lactams, cross-linked polyethylene oxides, polyacrylic acid, polyethylene oxide, polyacrylamides, starch graft copolymers etc.

Optionally, the push layer also comprises an osmotically active low molecular weight excipient which is physiologically acceptable, such as magnesium sulfate, magnesium chloride, sodium chloride, lithium chloride, potassium sulfate, sodium carbonate, sodium sulfite, lithium sulfate, potassium chloride, sodium sulfate, mannitol, urea, sorbitol, inositol, raffinose, sucrose, glycose, mixtures thereof, and the like. The excipient may be incorporated as particles, powder, or granules, and the like. Presently preferred are sodium chloride, magnesium salts, sugars, and sugar alcohols.

A particular advantage of the push-pull system is that the release profile of the active ingredient can be tailored to achieve nearly constant release rates over time regardless whether a soluble or poorly soluble form of pramipexole is selected for the composition of the invention. In the case of a water-soluble form, such as pramipexole dihydrochloride monohydrate, the imbibed water will dissolve much of the incorporated dose, and the drug is expelled from the delivery system in form of an aqueous solution. If a poorly water-soluble form of pramipexole is selected, the expelled form may be predominantly an aqueous suspension of the drug. Another particular advantage is that a pH independent release profile can be achieved, in particular if a non-ionic hydrogel-forming polymer is selected as one of the major constituents of the push layer.

Another embodiment of the present invention refers to an osmotic delivery system in that preferably the immediate release dose fraction of pramipexole is 0%. The rate of drug release is then constant or nearly constant over a period of at least 4 hours, and preferably over at least about 6 hours, at least about 8 hours, 10 hours, 12 hours, 16 hours, or 20 hours, or overabout 24 hours, respectively.

The push and pull layers are preferably manufactured as a bilayer tablet, using conventional layer tableting equipment. Subsequently, the bilayer tablet is coated with

the semipermeable coating, which is preferably applied onto the tablet core as an organic solution. Depending on the nature of the polymer and the amount which must be coated onto the tablet, the removal of the organic solvent must be carefully conducted over a sufficiently long period of time. For example, cellulose acetate is not readily soluble in organic solvents having a low toxicity, and must usually be dissolved in otherwise less preferred solvents such as methylene chloride. With the given film thickness which is needed to achieve the appropriate rate of water influx, which is preferably in the range from about 0.01 to about 0.5 mm and particularly from about 0.04 to about 0.25 mm, the drying time should be selected to be at least about 2 hours at 45 °C or higher, and in some cases even longer drying times such as at least 4 hours, 6 hours, 12 hours, 24 hours, or even longer should be chosen.

After drying the film coating, the at least one aperture, or orifice, is introduced, either by precision drilling or, more preferably, by laser drilling. The preferred diameter of the orifice is below 1 mm, and more preferably from about 0.05 to about 0.8 mm, or even from about 0.1 to about 0.6 mm.

Another osmotic system design according to the invention is a system in that the immediate release dose fraction of pramipexole in the composition is different from 0%, i.e. if a substantial amount of active ingredient, such as 20% to 50%, is to be incorporated in immediate release form, is that of an osmotic tablet which comprises at least two coatings, wherein at least one of the coatings comprises the immediate release fraction.

A particularly useful delivery system of this type comprises a compressed core comprising pramipexole and an osmotic agent. A semipermeable membrane having a preformed orifice or passageway surrounds the core; it is permeable to water and gastrointestinal fluid, but substantially impermeable for pramipexole. The membrane is covered partially or substantially completely by an inert, completely erodible water soluble polymer coat preferably comprising copolymer of vinylpyrrolidone and vinyl acetate. Furthermore, the devices comprises an external coat comprising an immediate release portion of pramipexole. The extended release dose fraction is released from the core after the polymer coat has partially or completely dissolved or eroded.

According to this embodiment, the semipermeable membrane is preferably based on cellulose acetate, and optionally also comprises a polyethylene glycol. The membrane is preferably applied onto the tablet core as a liquid polymer solution or suspension using a conventional coating technique. The drug-containing outer layer is also preferably applied as a polymeric film coating, for which reason its maximum drug load is limited. In the case of pramipexole, it is preferred that the outer coating layer comprises not more than about 1 mg of active ingredient, calculated as pramipexole dihydrochloride monohydrate, and more preferably not more than about 0.5 mg or 0.25 mg, respectively.

Another type of osmotic delivery system for oral therapy according to the invention is a device comprising only one homogeneous core compartment and one semipermeable membrane, in which the core is formulated with certain excipients which have been optimised for low-cost production. In particular, the core comprises at least two different hydroxyalkylcellulose polymers (or polymer grades), at least one sugar alcohol, and at least one mono- or disaccharide.

An example of a useful hydroxyalkylcellulose is hydroxyethylcellulose, which is available in different grades and should be incorporated to constitute about 5 to about 20 % of the core weight. Preferably, the hydroxyethylcellulose represents a mixture of a low substituted and a highly substituted grade of the polymer.

The saccharide is preferably selected from glyceraldehyde, threose, erythrose, lyxose, xylose, arabinose, ribose, talose, galactose, idose, gulose, mannose, glucose, altrose, xylulose, tagatose, sorbose, psicose, hamamalose, allose, the corresponding ketoses and deoxy forms, sedoheptulose, maltose, lactose, sucrose, cellobiose, isomaltose, and mixtures of any of these. The sugar alcohol may, for example, be selected from mannitol, sorbitol, galactilol, inositol, and xylitol. One of the preferred sugar alcohols is mannitol.

A useful content of the combined saccharide and the sugar alcohol in the core composition is at least about 10 wt.-% of the core, and preferably about 15 to 65 wt.-%. The ratio of saccharide to sugar alcohol is preferably selected in the range from about 1 : 10 to about 10 : 1.

The membrane is composed in a similar fashion as previously discussed for other types of osmotic systems. For example, it may be composed of cellulose acetate and polyethylene glycol. Preferably, the content of the polyethylene glycol is less than about 15 % relative to the weight of the dry membrane.

This formulation technique is selected to carry out the invention, it is preferred that the total dose of pramipexole is incorporated in extended release form, i.e. with 0% of the dose being in immediate release form. According to another preference, a less water-soluble form of pramipexole than pramipexole dihydrochloride monohydrate is selected as active ingredient.

Another embodiment of the present invention in form of an osmotic delivery system suitable for formulating Pramipexole comprises elements of the single-composition osmotic technology (SCOT). Surprisingly, it has been found that the basic principles of SCOT may be applied to the formulation of pramipexole, if all of the pramipexole dose is incorporated as an extended release form. In this case, the predetermine duration of drug release is preferably selected in the range of at least about 10 hours, and more preferably in the range from about 12 to about 24 hours.

According to this embodiment, pramipexole is incorporated within a tablet core which is prepared from granules comprising an excipient mixture which includes an osmotically active material. Similar to other osmotic delivery technologies, the tablet core is subsequently coated with a polymeric coating which is semipermeable, and which allows the uptake of water into the core, whereby its pressure increases.

In contrast to other osmotic tablets, a tablet prepared according to this embodiment does not comprise an orifice or aperture in its coating. If the internal pressure will reach a threshold, the membrane will break and form at least one passageway by which the dissolved or suspended drug substance is expelled or extruded from the core compartment. The shape of the tablet core is preferably adjusted to obtain a weak portion of the coating in order to avoid long lag phases before drug release through the aperture of the break which is formed in situ can commence.

According to another embodiment, the passageway through the membrane coating of the osmotic tablet is preformed in situ in the form of multiple microchannels or micropores. These pores are created by the dissolution of a soluble excipient, a small

amount of which is suspended in the film coating composition from which the semipermeable membrane is made.

In particular, it is preferred that the pore-forming excipient is selected from urea, magnesium sulfate, magnesium chloride, citric acid sodium chloride, potassium sulfate, sodium carbonate, lithium sulfate, calcium bicarbonate, sucrose, sodium sulfate, calcium lactate, potassium acid phosphate, magnesium succinate, and mixtures of any of these. Preferably, the pore-forming agent is suspended in a membrane based on an insoluble cellulose derivative, such as cellulose acetate, to which a plasticiser has been added.

The core may be formulated as described above, preferably incorporating a water-swellable, hydrogel-forming polymer such as hydroxypropyl methylcellulose and/or polyethylene oxide.

If this dosage form design is selected to practise the invention, it is recommended but not required that the dose fraction of pramipexole which is incorporated in extended release form is about 100 wt.-%. If the extended release fraction is selected to be substantially less than 100%, it is preferred that a further outer coating is added to the dosage form which accommodates the immediate release dose fraction of pramipexole, which should preferably be not more than about 1 mg per unit, and more preferably not more than about 0.25 mg, calculated as pramipexole dihydrochloride monohydrate.

According to a yet further embodiment, an osmotic delivery system for pramipexole is prepared without the use of a swellable, hydrogel-forming polymer which forces the drug out of the reservoir through an aperture or passageway. Instead, this embodiment uses only osmotic agents and osmotic pressure to release the active compound. The osmotic pressure is preferably exerted by a sugar alcohol, in particular sorbitol and/or mannitol.

Within this embodiment, it is further preferred that a "wicking" agent which provides enhanced flow channels for the dissolved pharmaceutical agent is incorporated. The wicking agent, defined as any material with the ability to draw water into the porous network of a delivery device, is included in the core of the tablet formulation. Both swellable and non-swellable wicking agents exist, but those that are preferably used in the composition are non-swellable wicking agents, such as colloidal

silicon dioxide, kaolin, titanium dioxide, fumed silicon dioxide, alumina, niacinamide, sodium lauryl sulfate, low molecular weight polyvinyl pyrrolidone, m-pyrol, bentonite, magnesium aluminium silicate, polyester, polyethylene. Materials particularly suitable include sodium lauryl sulfate, colloidal silicon dioxide, and low molecular weight polyvinylpyrrolidone.

If a poorly water soluble form of pramipexole is selected, it is also preferred that a solubilising agent is incorporated within the core formulation, such as an agent that inhibits crystal formation of the pharmaceutical or otherwise acts by complexation therewith, or a high HLB (hydrophilic-lipophilic balance) micelle-forming surfactant, in particular an anionic surfactants, or a citrate ester. According to another preference, combinations of any of these are included, particularly combinations of a complexation agent with an anionic surfactant.

Examples of agents that inhibit crystal formation of the pharmaceutical or otherwise act by complexation therewith include polyvinylpyrrolidone, polyethylene glycols such as PEG 8000, cyclodextrins and modified cyclodextrins. Examples of the high HLB, micelle-forming surfactants include non-ionic and/or anionic surfactants, such as Tween 20, Tween 60 or Tween 80; polyoxyethylene or polyethylene-containing surfactants, or other long chain anionic surfactants, particularly sodium lauryl sulfate. Examples of citrate ester derivatives that are preferred are the alkyl esters, particularly triethyl citrate. Preferred combinations of solubilising excipients are those of complexation agents and anionic surfactants, such as combinations of polyvinylpyrrolidone with sodium lauryl sulfate, or polyethylene glycol with sodium lauryl sulphate.

As an alternative to the osmotic tablet design which relies on passageways, aperture, or orifices for allowing pramipexole to be released from the dosage unit, it is also possible to coat a tablet which is slightly permeable to pramipexole, so that drug release can occur by diffusion through the coating. One of the advantages of this rather simple approach is that the manufacture of the product is very cost-effective, and that ample methods, equipment, and polymeric film-forming agents are available to design and produce such coated tablets in high volumes at a high quality.

Extended release polymeric coatings can be applied to various types of tablet cores. Preferably, the core comprises the complete dose of pramipexole, such as from about 0.375 mg to about 4.5 mg, calculated as pramipexole dihydrochloride monohydrate, and more preferably from about 0.375 mg to about 1.5 mg. Particularly preferred is a content of about 0.75 mg.

The tablet core should preferably have a shape which facilitates the application of a polymeric coating. Instead of being flat, it should be biconvex or oblong, and may exhibit a bevelled edge.

Suitable polymers for formulating extended release coatings are generally known to a person trained in the field. They include in particular ethylcellulose, insoluble methacrylate ester copolymers such as ethyl acrylate-methyl methacrylate copolymer (e.g. Eudragit RS and RL, Kollicoat EMM 30 D), and polyvinyl acetate (e.g. Kollicoat SR 30 D). The coating composition preferably comprises a plasticiser, such as a polyol, e.g. glycerol, propylene glycol, polyethylene glycol (preferably PEG 200-6000); an organic ester, e.g. diethyl phthalate, dibutyl phthalate, dibutyl sebacate, triethyl citrate, acetyltriethyl citrate, acetyltributyl citrate, tributyl citrate, triacetin; or an oil, e.g. castor oil, distilled acetylated monoglycerides, fractionated coconut oil, and the like.

Optional further excipients of the coating composition include pigments, opacifiers, surfactants, sweetening agents, flavours, adhesion enhancers, anti-foaming agents, anti-tacking agents, stabilisers, antioxidants, etc.

One of the preferred coating compositions for film-coated tablets comprises from about 20 to 85 wt.-% of a water-insoluble, water-permeable film-forming polymer, about 10 to 75 wt.-% of a water-soluble polymer and about 5 to 30 wt.-% of a plasticiser. In this embodiment, it is also preferred that the water-insoluble, water-permeable film-forming polymer is ethylcellulose, the water-soluble polymer is polyvinylpyrrolidone or hydroxypropylcellulose, and the plasticiser is stearic acid.

The coating is preferably applied onto a pramipexole-containing tablet core to a thickness by virtue of which the dosage unit exhibits a dissolution profile such that after 2 hours, from 5 to 40 % of the incorporated pramipexole is released, after 4 hours, from 10 to 60 %, after 12 hours, from 50 to 98 %, and after 24 hours, more than 80% of the pramipexole is released.

The coating can be applied onto the tablet core by any conventional coating technique, but the settings of certain parameters such as the spray rate of the coating liquid and the temperature of the drying air depends on the specific formulation and on whether an aqueous or an organic solvent is used for the coating solution or suspension. For an aqueous polymeric dispersion, it is recommended that the coating temperature during the application process should be about 10-20°C above the minimum film-forming temperature in order to ensure the optimum conditions for film formation. In contrast, the application of an organic coating solution can also be carried out at a somewhat lower temperature, such as in the range from about 30 to 45 °C, if this is desired for the sake of product stability.

In a further embodiment, the film coating is designed to comprise more than one layer. For example, the coating may consist of an inner and an outer layer, wherein the inner comprises a water-soluble and swellable polymer or a blend of polymers, and the outer layer comprises a water-insoluble polymer or a blend of polymers. The polymer or polymers of the inner layer are preferably selected from hydroxypropylcellulose, hydroxypropyl methylcellulose, polyvinyl alcohol, and polyvinyl pyrrolidone, whereas the outer layer is preferably based on ethylcellulose, optionally blended with another, per se more water soluble, cellulose ether.

It has been found that a nearly zero order release profile can be achieved by adjusting the thicknesses and permeabilities of the layers so as to cause the diffusion of the active ingredient through the inner layer to be the rate controlling step. In this case, care must be taken to provide the outer layer with sufficient elasticity and flexibility to prevent its rupture due to the swelling of the inner layer, such as by incorporating an appropriate plasticiser or mixture of plasticisers into the outer layer.

Another method of applying coatings to the tablet cores according to the present invention turned out to be electrostatic powder deposition method. This method requires that the tablet core and the powder formulation for the coating are electrically chargeable. During deposition, an electric field is applied by which the powder particles are attracted onto the tablet surface. Subsequently, the powder coating must be fused by the application of heat in order to form a membrane.

To obtain good results, the dry powder preferably has the following physical properties: (1) A particle size in the range of 1 μm to 1000 μm and preferably in the range of 30 μm to 80 μm; a small particle size enables the powder to be evenly dispersed in the region to which it is supplied; (2) A relatively high resistivity in the range of 10^6 Ωm to 10^{24} Ωm and preferably in the range of 10^{10} Ωm to 10^{14} Ωm; such high resistivity facilitates maintenance of the powder charge but makes it harder to charge the powder; (3) A viscosity when in the liquid phase of less than 500 Pas and preferably less than 75 Pas; such low viscosity facilitates even spreading of the coating over the surface of the tablet core; (4) After conversion to a fused film, a tensile strength of more than 0.5 N/m^2 and preferably more than 3.5 N/m^2, as a reasonably strong and tough coating is required in order to protect the tablet during subsequent handling up to the administration of the tablet; (5) A melting point which lies in the range of 50 °C to 180 °C and preferably 60 °C to 100 °C. With a relatively low melting point, less energy is required to convert the powder into the liquid phase and the risk of damage to the tablet core from heating is reduced. This is of particular importance if a temperature-sensitive form of pramipexole is selected as active ingredient.

Examples of materials which, alone or when blended with other materials, meet some or all of the five preferred properties listed above can be found among polyamides, polyalkenes, waxes, oils, polyesters, sugar alcohols, sugars, polyoxyethylenes and ethylene vinyl acetate copolymer. Examples of particularly suitable sugar alcohols are sorbitol and xylitol. Examples of suitable sugars are sucrose and lactose.

The powder deposition step is preferably carried out by using a conveying means to hold and transport the tablet core. More in detail, the preferred method involves feeding the tablet cores onto a conveying means, providing an electrode spaced above the conveying means and extending along and across the conveying means to define a box-like region between the electrode and the conveying means, and maintaining the electrode at a first electric potential, supplying the coating material to the box-like region and electrically charging the coating material to a second electric potential, conveying the tablet cores on the conveying means through the region with the conveying means and/or the substrates maintained at a different electric potential from

the coating material and the electrode, whereby the coating material is attracted to the exposed surfaces of the tablet cores.

The dry powder coating is converted into a fused film by heating, preferably by infrared radiation, but other forms of electromagnetic radiation may also be used. Alternatively, the conversion into a fused film may be achieved partly or wholly by reducing the pressure of the region. Usually the change in the coating upon heating will simply be a physical change from a powder to a liquid and then, on cooling, to a continuous solid coating, but there are other possibilities: for example, the powder coating may comprise a polymer which is cured during the treating step, for example by irradiation with energy in the gamma, ultra violet or radio frequency bands, to form a continuous cross-linked polymer coating.

Using this powder deposition technique, it is possible to produce tablets which are completely coated with an extended release coating through which pramipexole is release by diffusion in the dissolved state; but it is also possible to design special tablet configurations which will effect selected release profiles including zero-order release, pulsed release, or other patterns of pramipexole release.

According to one of the embodiments, electrostatic powder deposition is used to make a coated tablet in which essentially the complete dose of pramipexole is in extended release form, and wherein the release profile is linear or nearly linear. In another embodiment, the immediate release fraction of the dose of pramipexole is substantially different from 0 wt.-%, in particular in the range from about 20 wt.-% to about 50 wt.-%; in this embodiment, the extended release fraction is incorporated in the tablet core and the immediate release fraction is coated onto the tablet core by powder deposition. Preferably, the pramipexole-containing coating is protected by a further, outer coating layer which is drug-free.

In another embodiment, the composition of the invention is designed as a tablet which has no extended release coating. In other words, the extended release is effected by the composition of the core itself, and while the tablet may be coated, the coating does not affect drug release to a major extent. This embodiment is different from the previously described uncoated tablets which disintegrate shortly after administration

into multiple units, such as extended release pellets or microtablets, as in the present case the core itself is an extended release matrix which does not disintegrate rapidly.

Extended release matrix tablets are hydrophilic or lipophilic in nature. In one of the preferred embodiments, the composition of the invention is designed as a hydrophilic matrix tablet. A matrix tablet, in the context of extended release, should be understood as a semisolid or, more typically, a solid form in which the active ingredient, introduced as powder or granules, is relatively homogeneously distributed.

The design of a matrix tablet is particularly useful if the immediate release fraction of pramipexole is selected to be 0% of the incorporated dose. On the other hand, also an immediate release dose fraction can be accommodated, for example in form of a drug-containing soluble coating layer which is applied onto the matrix tablet.

Various excipients and formulation techniques may be used to make a hydrophilic pramipexole extended release matrix with a defined fraction of the active ingredient being in extended release form. Generally speaking, a hydrogel-forming polymer is required to formulate this type of tablet. The polymer may or may not exhibit pronounced swelling in aqueous media. It must be capable of forming a viscous or gelled, partially soluble or insoluble network of hydrophilic macromolecules, held together by physical or chemical entanglements, by ionic or crystalline interactions, by complex formation, by hydrogen bonds or van der Waals forces. A hydrophilic matrix releases its incorporated active ingredient slowly, gradually, continuously over time either by diffusion through the polymeric network, by erosion of a superficial gel layer, by dissolution of the polymer, or by a combination of any of these mechanisms.

Suitable polymers for making a hydrophilic matrix include, for example, alkylcelluloses, such as, methylcellulose; hydroxyalkylcelluloses, for example, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose and hydroxybutylcellulose; hydroxyalkyl alkylcelluloses, such as, hydroxyethyl methylcellulose and hydroxypropyl methylcellulose; carboxyalkylcelluloses, such as, carboxymethylcellulose; alkali metal salts of carboxyalkylcelluloses, such as, carboxymethylcellulose sodium; carboxyalkyl alkylcelluloses, such as, carboxymethyl ethylcellulose; carboxyalkylcellulose esters; other natural, semi-synthetic, or synthetic di-, oligo- and polysaccharides such as trehalose, alginic acid, alkali metal and

ammonium salts thereof, carrageenans, galactomannans, tragacanth, agar, acacia, guar gum and xanthan gum, pectins such as sodium carboxymethyl amylopectin, chitin derivates such as chitosan, polyfructans, inulin; polyacrylic acids and the salts thereof; polymethacrylic acids and the salts thereof, methacrylate copolymers; polyvinyl alcohol; polyvinylpyrrolidone, copolymers of polyvinylpyrrolidone with vinyl acetate; combinations of polyvinyl alcohol and polyvinylpyrrolidone; polyalkylene oxides such as polyethylene oxide and polypropylene oxide and copolymers of ethylene oxide and propylene oxide.

One of the particularly suitable hydrophilic matrix-forming polymers is cross-linked amylose, in particular amylose which has been cross-linked with a cross-linking agent selected from the group consisting of epichlorohydrin and 2,3-dibromopropanol, and wherein the cross-linked amylose is prepared by cross-linking amylose with from 0.1 to 20 grams of said cross-linking agent per 100 grams of amylose, and especially from 0.5 to 10 grams of cross-linking agent per 100 grams of amylose. It has been found that this polymer is capable of being compressed into tablets which pramipexole, which tablets, upon immersion in an aqueous medium, form a strong hydrogel which exhibits substantial swelling, but which is also mechanically resistant to withstand the grinding forces exerted by the muscular wall of the gastrointestinal tract. Therefore, the chances that the dosage unit is affected in its performance by different patterns of gastrointestinal motor activity is minimised, and at least one factor of performance variability is substantially excluded.

If crosslinked amylose is selected as matrix-forming agent, it is also preferred that the content of this excipient in the tablet is from about 30 to about 90 wt.-%, in particular from about 50 to about 85 wt.-%. Powders containing 0.375 to 4.5 mg pramipexole, calculated as pramipexole dihydrochloride monohydrate per dosage unit, and the preferred content of crosslinked amylose in an appropriate particle size, such as from about 25 to about 700 µm in average, or more preferably from about 50 to 500 µm, and further optional excipients such as a dry binding agent and/or a lubricant, can usually be compressed directly without prior granulation, preferably at compression forces of at least about 0.15 T/cm^2.

Optionally, crosslinked amylose is used in combination with at least one further hydrogel-forming excipient, which is preferably selected from the group of hydrophilic

cellulose ethers, in particular from hydroxyalkyl cellulose derivatives such as hydroxypropyl methylcellulose. One of the particularly suitable compositions according to this embodiment comprises from about 0.375 to 1.5 mg pramipexole, calculated as pramipexole dihydrochloride monohydrate per dosage unit, mixed and compressed with at least 40 wt.-% of a matrix-forming polymer mixture containing from 30 to 90 wt.-% (relative to the composition) cross-linked amylose and from 10 to 30 wt.-% of hydroxypropyl methylcellulose having a viscosity equal to or higher than 4000 cps. As used herein, the viscosity of a polymer is defined as the viscosity of its 2 % (W/V) aqueous solution at 20 °C, unless stated otherwise. Suitable grades of hydroxypropyl methylcellulose include in particular HPMC 2208 and HPMC 2910.

With respect to further inactive ingredients which may be needed for tableting, the following preferences exist: Fillers, such as lactose or sucrose, should be incorporated in quantities not exceeding about 40 wt.-%. Glidants, such as silicon dioxide, should be incorporated in amounts of less than about 5 wt.-%, in particular less than about 3 wt.-%. Lubricants and anti-adherents, such as magnesium stearate, may be incorporated in quantities not exceeding about 5 wt-%, and preferably not exceeding about 3 wt.-%.

In another embodiment, a hydrophilic matrix comprising pramipexole is formulated on the basis of a polymer mixture comprising a heteropolysaccharide and a polysaccharide gum which is capable of cross-linking the heteropolysaccharide in the presence of water. This formulation technique, which is also known as the TimeRx technology, has been found to work particularly well for pramipexole if the heteropolysaccharide is selected from xanthan gum and derivatives of xanthan, and if the cross-linking polysaccharide comprises a galactomannan, in particular locust bean gum. The ratio between the two polysaccharide components is very roughly from about 3 : 1 to 1 : 3, or even about 1 : 1.

Optionally in combination with an inert filler such as inert a monosaccharide, a disaccharide, or a polyhydric alcohol, as for example lactose, dextrose, sucrose, fructose, microcrystalline cellulose, xylitol, and/or sorbitol, the polymer mixture can be granulated to yield a free-flowing, compressible excipient mixture with which the active compound is mixed and compressed into a matrix tablet. Preferably, the granules have a predominant particle size ranging from about 100 to about 400 µm, in particular from about 150 to about 350 µm. Preferably, the content of the combined polymers in the

granules is from about 20 to about 60 wt.-%, and the content of the inert filler is from about 40 to about 80 wt.-%. The ratio of the inert filler to the combined polymers is preferably from about 4:1 to about 0.67:1.

Another embodiment of the present invention refers systems comprising soluble forms of pramipexole, such as pramipexole dihydrochloride monohydrate, together with a mixed hydrophilic-hydrophobic matrix, in which a hydrogel-forming polymer is used to create a microenvironment for the active compound within an otherwise hydrophobic matrix. For example, a hydrophilic polymer may be selected from the group of crosslinked acrylic acid polymers (e.g. Carbomer 934P), block copolymers of ethacrylic and methacrylic acid esters or copolymers of methacrylic acids (e.g. Eudragit RL and RS), anionic and cationic copolymers of methacrylic acids and -acid esters (e.g. Eudragit S and E), hydroxyethyl methacrylic acid polymers and hydroxymethyl methacrylic acid polymer.

The hydrophobic matrix component may, for example, be selected from selected from the group consisting of glyceryl monostearate, mixtures of glyceryl monostearate and glyceryl monopalmitate, glyceryl monooleate, mixtures of mono, di and tri-glycerides, glyceryl monolaurate, paraffin, white wax, long chain carboxylic acids, long chain carboxylic acid esters and long chain carboxylic acid alcohols. More specifically, the long chain carboxylic acid is preferably n-dodecanoic acid, n-tetradecanoic acid, n-hexadecanoic acid, caproic acid, caprylic acid, capric acid, lauric acid, myristic acid, palmitic acid, stearic acid, arachidic acid, behenic acid, montanic acid, melissic acid, oleic acid, gadoleic acid, erucic acid, linoleic acid, linolenic acid, arachidonic acid, behenolic acid or diacetyl tartaric acid.

Furthermore, it is useful to incorporate a binder, such as acacia, corn starch paste, modified or pre-gelatinised starches and dextrose, hydroxypropyl methylcellulose, hydroxypropylcellulose, ethylcellulose, gum arabic, tragacanth or guar gum. Optionally, the tablet formulation further comprises an inorganic filler, such as calcium phosphate dihydrate or calcium sulfate, and minor amounts of further excipients such as glidants, pigments, and anti-adherents.

Another embodiment for water-soluble forms of pramipexole involves the granulation of pramipexole with two or more polymers or gums of differing swelling

characteristics. The differential hydration rates of each polymer may be combined to suppress the diffusion of the imbedded drug for up to 24 hours.

In particular, the tablet matrix is based on a singular polymer matrix of a polymer which is swellable and erodible, and a plurality of granules embedded within and dispersed throughout the polymer matrix. The granules comprise a polymer which is swellable and the fraction of pramipexole selected to be in extended release form. Importantly, the polymer of the matrix is more swellable and erodible than the polymer of the granules, and preferably the polymer matrix has a diffusion rate coefficient greater than the diffusion rate coefficient of the granules. The matrix-forming polymer may be selected from HPMC, polyethylene oxide, and mixtures of HPMC and pectin, whereas the polymer of the granules is selected from gelatin, gum tragacanth, and pectin. A preferred mixture of HPMC and pectin has a weight ratio between pectin and HPMC in the range from about 2:7 to 4:5.

Optionally, an immediate release dose fraction which is substantially different from 0% of the total incorporated dose of pramipexole is incorporated in the matrix tablet as powder, and not as part of the polymer granules.

A further formulation technique in context with the current invention makes use of "salting-out" phenomenon to moderate the swelling and erosion kinetics of a non-ionic polymer matrix containing pramipexole and one or more electrolytes. The presence of these electrolytes allows for the generation and maintaining of effective diffusion channels. The electrolyte excipients also contribute to a contracting micro-environment within the tablet, whose pH is influenced by the pKa of the electrolyte, which may increase or decrease the solubility of the active ingredient. As the matrix hydrates, the electrolytes and the polymer compete with the active ingredient for hydration water, resulting in a predetermined release profile. The technology is particularly suitable for those active agents whose degree of solubilisation is substantially independent of pH over the range of pH 1.5 to pH 7 .5, which is the case at least for the highly water-soluble forms of pramipexole.

In particular, a monolithic tablet prepared according to this formulation technique comprises a hydrophilic swellable polymeric matrix in which the water soluble form of pramipexole is dispersed, and an inorganic salt which is also dispersed in the matrix,

preferably at a concentration in the range of 50 to nearly 100 wt.-% weight of the polymeric matrix. The type and quantity of the salt is selected to, upon exposure to an aqueous medium, cause a hardened boundary around the periphery of the matrix. The inorganic salt may be selected from sodium chloride, sodium bicarbonate, potassium bicarbonate, sodium citrate, sodium bisulfate, sodium sulfite, magnesium sulfate, calcium chloride, potassium chloride, and sodium carbonate. The hydrophilic, swellable matrix-forming polymer is preferably hydroxypropyl methylcellulose or polyethylene oxide.

Because the dosage unit represents a non-covalently bonded matrix, the manufacturing process is essentially a two-step process of dry-blending and direct compression. The simple process allows for the cost-effective and efficient manufacture of monolithic tablets.

Alternatively, the composition of the invention may be formulated as a tablet which is composed of a plurality of granules comprising the active compound, i.e. pramipexole, at least one amino acid, an intragranular polymer which accounts for about 4 to 45 wt.-% of the dosage form unit, and a hydrophilic extragranular polymer in which the granules are dispersed. The extragranular polymer represents about 4 to 47 wt.-% of the dosage form unit and is selected to be more rapidly hydrating that the intragranular polymer. The amino acid is selected for hydropathy characteristics depending on solubility characteristics of the active compound and accounts for about 11 to 29 wt.-% of the total tablet. Examples of preferred amino acids include glycine, alanine, valine, leucine, isoleucine, phenylalanine, proline, aspartic acid, glutamic acid, lysine, arginine, histidine, serine, threonine, cysteine, asparagine and glutamine. If a water soluble form of pramipexole is selected, such as pramipexole dihydrochloride monohydrate, a relatively hydrophilic amino acid should be selected.

The intragranular polymer is preferably one or more of polyethylene oxide, polyvinyl acetate, a galactomannan polysaccharide selected from the group consisting of hydroxypropyl guar, guar gum, locust bean gum, pectin, gum acacia, tragacanth and karaya gum, and a cellulose ether. A particularly preferred intragranular polymer is a galactomannan polysaccharide. The extragranular polymer is preferably selected from polyethylene oxide, a galactomannan polysaccharide selected from the group consisting of hydroxypropyl guar, guar gum, locust bean gum, pectin, gum acacia, gum tragacanth

and karaya gum, and cellulose ethers. A particularly preferred extragranular polymer is guar gum.

In a yet further embodiment, the composition is based on certain matrix-forming polymeric excipients representing a mixture of polymers of which at least one is hydrophilic. For example, one of the preferred carriers according to this embodiment is a blend of hydroxypropyl methylcellulose and shellac. Another suitable matrix-forming polymer mixture is that of xanthan and hydroxypropyl methylcellulose.

Another suitable extended release matrix tablet composition comprises a hydrogel-forming polymer selected from hydroxypropyl methylcellulose, sodium alginate and xanthan and a non-toxic, pharmaceutically acceptable ionisable excipient selected from alkali metal chlorides, organic acids, alkali metal sulfates and alkali metal alkyl sulfates, dihydrogen sodium phosphate and monohydrogen sodium phosphate. More preferably according to this embodiment, the hydrogel-forming polymer is hydroxypropyl methylcellulose, and the ionisable excipient is disodium hydrogen phosphate, sodium chloride, or a mixture of sodium chloride and sodium lauryl sulfate.

In a further preferred composition, a water soluble form of pramipexole is embedded in a compressed matrix comprising from about 20 to about 60 wt.-% of a low molecular weight hydroxypropyl cellulose having a number average molecular weight of 70,000 to 90,000, from about 4 to about 10 wt.-% of a high molecular weight hydroxypropyl cellulose having a number average molecular weight of 1,100,000 to 1,200,000, and an inert solid diluent, such as sucrose, mannitol, sorbitol, lactose and dextrose.

Moreover, so-called intelligent polymers may be used as matrix-forming agent. According to this embodiment, the mechanism of release involves the swelling of the polymers within the matrix, which enables the drug to be dissolved and released by diffusion through an unstirred boundary layer. Typically, the release profile follows first order kinetics, and can be tailored to provide up to at least about 20 hours of pramipexole release.

If this approach is selected to formulate pramipexole, it is required that a form of pramipexole is chosen which exhibits a water contact angle θ which characterised by a $\cos\theta$ between +0.9848 and -0.9848. Furthermore, the matrix comprises a first

intelligent polymer component comprising ethyl cellulose and a second intelligent polymer component which has opposite wettability characteristics to the first intelligent polymer component. Preferably, the second intelligent polymer component is a mixture of hydroxyethylcellulose and hydroxypropyl methylcellulose. The ethylcellulose content of the formulation is preferably at least 5 wt.-%. The weight ratio between the first and second polymer components is in the range of about 1:100 to about 100:1. Thus, the composition comprises two groups of polymers having opposing wettability characteristics, one demonstrating a stronger tendency towards hydrophobicity (i.e. ethylcellulose) and the other possessing a stronger a tendency towards hydrophilicity.

Optionally, such a formulation of pramipexole further comprises a channel-forming excipient, such as anhydrous lactose, at a content of about 10 to 70 wt.-%, and a compression enhancer, which is preferably microcrystalline cellulose, and which may be present at an amount of about 5 to 30 wt.-%.

According to a yet further embodiment, the pramipexole-containing composition of the invention comprises a non-porous matrix which is not prepared by the compression of a powder or granules, but by melt extrusion. Melt extrusion methods are well-established in chemical engineering, but can be adapted to the manufacture of pharmaceutical formulations in a single, continuous process. To make melt-extruded forms, pramipexole is mixed with, or optionally dissolved in, a thermoplastic polymer or mixture of polymers together with further excipients, if required. The mixture is then extruded and shaped like tablets, optionally also as granules, pellets, sheets, or other forms.

If a melt-extruded dosage form design is selected for pramipexole, the matrix-forming polymer may be selected from water-soluble polymers with a glass transition temperature of less than about 175 °C such as alkylcelluloses, e.g. methylcellulose, hydroxyalkylcelluloses, e.g. hydroxymethyl-, hydroxyethyl-, hydroxypropyl- and hydroxybutylcellulose, hydroxyalkyl alkylcelluloses, e.g. hydroxyethyl methylcellulose and hydroxypropyl methylcellulose, polyvinylpyrrolidone, copolymers of N-vinylpyrrolidone and vinyl acetate containing up to 50% by weight of vinyl acetate, carboxyalkylcelluloses such as carboxymethylcelluloses, polysaccharides such as alginic acid and their alkali metal and ammonium salts; preferably in combination with

a less water soluble polymer, in particular with a low-substituted grade of hydroxypropyl cellulose.

More preferably, the glass transition temperature of the water soluble polymer is not higher than about 165 °C so as to ensure that the polymer softens and can be extruded at a temperature in the range from about 55 °C to about 160 °C. The content of low-substituted hydroxypropyl cellulose, preferably having a degree of molar substitution of from 0.5 to 2, more preferably from 1.5 to 1.8, should be in the range from about 35 to about 90 wt.-%, relative to the dosage unit.

Further optional excipients include, for example, fillers, lubricants, anti-adherents, flow regulators, plasticisers, colorants and stabilisers. Examples of potentially useful fillers include oxides of magnesium, aluminium, silicon and titanium; mannitol, lactose, sorbitol, xylitol, pentaerythritol and the like, preferably incorporated to a content of up to about 20 wt.-%. Useful flow regulators include mono-, di- and triglycerides of fatty acids having 12 to 20 carbon atoms, waxes such as carnauba wax, and phospholipids, at an amount of about 0.1 to 7.5 wt.-%. Optional lubricants are, for instance, stearates of aluminium or calcium, or talc, at a level of about 0.1 to 3 wt.-%. Useful stabilisers include antioxidants, UV absorbers, and radical scavengers at a content from about 0.01 to 0.5 wt.-%.

In one of the particularly preferred embodiments, a plasticiser is present, optionally selected from low molecular weight polyalkylene oxides, e.g. polyethylene glycol, polypropylene glycol and polyethylene propylene glycol; polyhydric alcohols, e.g. propylene glycol, glycerol, pentaerythritol and sorbitol; sodium diethylsulfosuccinate, the mono-, di- and triacetate of glycerol and polyethylene glycol stearic acid esters, or mixtures of any of these. A preferred content range for the plasticiser or mixture of plasticisers is from about 0.5 to 15 wt.-%, such as about 0.5 to 5 wt.-%.

In a further embodiment, the extruded matrix comprises from about 5 to about 90 wt.-% of a melt-processable, water-soluble polymer, from about 5 to about 85 wt.-% of isomalt, and, optionally, up to about 5 wt.-% of a phospholipid component which is selected from natural and synthetic phosphatidylcholins and natural - optionally purified or hydrated - mixtures of phosphatidylcholins with other lipids, such as egg or soy

lecithin. In a yet further embodiment, the matrix comprises from about 10 to about 99 wt.-% of at least one water-soluble, melt-processable homo- or copolymer of N-vinylpyrrolidone and from about 1 to about 90 wt.-% of an at least partially hydrolysed or degraded starch component.

The melt extrusion process is preferably carried out using a single- or double screw extruder with at least 2 individually heatable temperature zones. Coated units may be prepared by coextruding two different compositions. In this way, it is also possible to prepare extruded compositions with two compartments, one of which comprising the extended release dose fraction of pramipexole, the other one comprising an immediate release fraction which is substantially different from 0% of the total incorporated dose. The separation of the individual dosage units can be accomplished, for example, with rotating knives.

In another principal group of embodiments, the pramipexole composition of the invention is designed as a hard capsule comprising either multiple extended release units, such as pellets, microparticles, granules, or minitablets, or a single matrix which may be hydrophilic or lipophilic in nature.

A monolithic matrix within a hard capsule may be prepared by mixing pramipexole with at least one meltable matrix-forming agent and, optionally, further excipients, heating the mixture above the melting temperature of the matrix-forming agent, filling the melt into the bottom part of a two-piece hard capsule, closing the capsule using the corresponding top half of the hard capsule, sealing it, and allowing the melt to solidify. Optionally, the melt solidifies before the capsule is closed.

To formulate a lipophilic matrix, a lipid or wax is preferably selected as matrix-forming agent which melts at a temperature of about 35 to about 90 °C, and more preferably from about 40 to about 75 °C. Suitable lipids include, for example, mono-, di- and triglycerides of medium and long chain fatty acids, whether natural or synthetic, including hydrogenation products of natural triglyceride mixtures, especially partially hydrogenated cottonseed oil, castor oil, soybean oil, and palm oil. Suitable waxes include, for example, beeswax, myricyl palmitate, petroleum wax, and microcrystalline wax. To formulate hydrophilic and amphiphilic matrices, a meltable polymer or polymeric surfactant preferably having a melting temperature of about 35 to about 90

°C, and more preferably from about 40 to about 75 °C is selected, such as from polyethylene glycols, polyethylene oxides, and ethylene oxide-propylene oxide copolymers. These meltable matrices which often are somewhat softer than compressed matrix tablets are also referred to as SSM's, or semi-solid matrix formulations.

Depending on the choice of excipients, in particular of the principal matrix-forming agent, the type of hard capsule should be selected to avoid incompatibilities between the capsule wall and the matrix. For example, if medium chain monoglycerides are comprised in the matrix composition, capsules made from gelatin should not be used. The same is true in the event that large amounts of hygroscopic materials are present in the formulation. In these cases, capsules made from alternative materials such as starch or, more preferably, hydroxypropyl methylcellulose should be selected.

Many of the meltable matrices which are suitable for hard capsules may also be filled into soft capsules, such as soft gelatin capsules. Therefore, the composition of the invention may optionally be designed as soft capsules filled with an extended release matrix formulation comprising pramipexole. However, the design of a hard capsule, tablet or extruded form is presently more preferred.

As mentioned above, it is one of the preferred embodiments that the hard capsules comprise a plurality of extended release units, such as extended release pellets, granules, microcapsules, or mini-tablets. These units are the components of the composition which predominantly control the extended release profile of pramipexole. The hard capsule itself preferably disintegrates upon contact with water or intestinal fluid within a period of less than about 60 minutes, and more preferably within less than about 30 minutes or even 15 minutes, respectively. The units comprise the dose fraction of pramipexole which is in extended release form.

If this dosage form design is selected, it is easily possible to accommodate an immediate release dose fraction of substantially more than 0 % of the total incorporated dose, such as 20 to 50 %, or from about 25 to about 33.3 %. The immediate release dose fraction may be incorporated, for example, as a powder component within the hard capsule, but external to the extended release units. Optionally, the immediate release fraction may also be incorporated in the form of a plurality of shaped units such as pellets, granules, or mini-tablets, which are not the same as the extended release units.

As used herein, pellets are agglomerated particles usually having a roughly spherical or spheroidal shape and, typically, a diameter in the range from about 300 µm to 3 mm. Pellets are sometimes also referred to as beads. Granules, as used herein, are agglomerated particles which may or may not be spherical or spheroidal, and which typically have a diameter in the range from about 50 µm to about 1 mm. It is not always possible to differentiate between pellets, beads, and granules.

Mini- or micro-tablets, on the other hand, are understood as units prepared by the compaction of powders or granules, and they may have various shapes. Typically, their diameters are in the range from about 1 to about 5 mm, in particular from about 1.5 to about 4 mm.

Microcapsules are particles of various shapes and morphologies prepared by different encapsulation methods. Usually they have a diameter in the range from about 1 µm to about 1 mm. Depending on their morphology, they may be referred to as microspheres, microparticles or microcapsules. Preferably, however, the extended release units used in the present invention are selected from units with a diameter of more than 1 mm, such as pellets or mini-tablets.

The multiple extended release units may be coated with a polymeric coating which is poorly soluble in water and which allows the slow release of dissolved pramipexole by diffusion through the hydrated polymeric coating. To achieve such coating, the same principles and preferences apply that have been described above in the context of extended release coatings for tablets. However, the smaller size and larger total surface area of the multiple units must be taken into consideration when composing the film coating. A tablet coating which would provide an appropriate release profile may not provide sufficient release control for a pellet formulation. In other words, if the same coating composition is to be used for pellets or mini-tablets, the thickness will typically have to be higher than in the case of larger tablets in order to produce the same effect. Alternatively, the composition of the coating may be adapted by increasing the level of a water insoluble, film-forming polymer such as methacrylic acid copolymer, ethylcellulose or cellulose acetate.

Optionally, the pellets are formed by layering pramipexole and a binder onto inert spherical beads, such as sugar beads. The binder may, for example, be selected from

povidone, pharmaceutical glaze, sugar, hydroxypropyl methylcellulose, hydroxypropylcellulose, ethylcellulose, acrylic and methacrylic acid co-polymers and mixtures thereof. The inert beads preferably account for about 15 to 40 wt.-% of the composition, and the binder from about 0.5 to 4 wt.-%. The drug-coated beads or pellets may be further coated with a layer of talc, the talc being present at an amount of about 4 to 20 wt.-% relative to the composition.

Furthermore, it is important that a further outer coating composed of a film-forming agent and a plasticiser is present to control the release of pramipexole. This outer coating comprises about 5 to 35 wt.-% of the composition. The film-forming agent may comprise a polymer selected from ethylcellulose, methylcellulose, hydroxypropylcellulose, cellulose acetate, hydroxypropyl methylcellulose, hydroxyethylcellulose, and mixtures of any of these. The plasticiser is preferably selected from diethyl phthalate, diethyl sebacate, triethyl citrate, crotonic acid, propylene glycol, castor oil, citric acid esters, dibutyl phthalate, dibutyl sebacate and mixtures thereof. The extended release pellets are preferably sieved or otherwise screened in order to obtain the preferred particle size fraction of -10/+60 mesh according to US standard mesh size.

According to this formulation option, an immediate release dose fraction of substantially more than 0% of the total dose of pramipexole may be incorporated in the form of pellets which have the same composition of the extended release pellets, except for the outer coating based on the film-forming polymer and the plasticiser. It has been found that by mixing an amount of about 0 to about 35 wt-% of immediate release pellets with an amount of about 65 to about 100 wt.-% of the extended release pellets, very smooth and nearly linear release profiles over up to approx. 24 hours can be obtained.

In a further embodiment, the multiple units comprise coatings having at least two layers, including a first layer which is based on an enteric polymer, and a second layer which comprises both a water-insoluble and an enteric polymer at a weight ratio of about 10:1 to 1:1. In this embodiment, the first layer may cover the second layer, or vice versa. The enteric polymer is preferably selected from esters of cellulose, polyvinyl acetate phthalate, pH-sensitive methacrylic-methyl methacrylate copolymers and shellac, whereas the water-insoluble polymer is preferably ethylcellulose, polyvinyl

acetate, a neutral copolymer based on ethyl acrylate and methylmethacrylate, or a copolymer of acrylic and methacrylic acid esters having quaternary ammonium groups. It is further preferred that at least one of the layers comprises a plasticiser such as triacetin, tributyl citrate, triethyl citrate, acetyl tri-n-butyl citrate, diethyl phthalate, castor oil, dibutyl sebacate, acetylated monoglycerides and mixtures thereof. The relative weight of the combined coating layers to the total pellets is from about 15 wt.-% or about 80 wt.-%, and preferably from about 20 wt.-% to about 65 wt.-%.

The pramipexole-containing cores of the multiple units are preferably non-pareil beads - e.g. made of sucrose - coated with pramipexole and polymeric binder, or pellets prepared by granulation and milling or by pellet extrusion-spheronisation. Alternatively, they may represent mini-tablets.

Another type of multiple units which may be used to practise the invention is designed as having a core containing pramipexole and one or more hydrophilic gelling polymers, coated with at least one water insoluble polymer membrane which is present at a content of about 5 to 30 wt. % based on the total weight of the coated dosage form. The water insoluble polymer is preferably selected from ethylcellulose, neutral copolymers based on ethylacrylate and methylmethacrylate, copolymers of acrylic and methacrylic acid esters with quaternary ammonium groups and combinations of any of these, optionally plasticised with one or more plasticiser such as triacetin, tributyl citrate, triethyl citrate, acetyl tri-n-butyl citrate diethyl phthalate, corn oil, castor oil, dibutyl sebacate, and acetylated monoglycerides. A particularly preferred hydrophilic gelling agent is hydroxypropyl methylcellulose. The cores may represent pellets or mini-tablets.

According to this embodiment, the core composition as well as the membrane thickness can be varied in order to achieve various release profiles, from rapid initial release rate changing to near zero order release profiles with or without a lag time. Without wishing to be bound by theory, it is believed that the drug release from this dosage form is controlled by dual mechanism, i.e. the dissolved drug first diffuses through the gelled polymer matrix and then through primarily a water insoluble polymer membrane. Since nearly all desired release profiles of pramipexole can be achieved by this just one type of multiple unit, it is preferred that the pramipexole dose fraction which is incorporated in the composition in immediate release form is 0%.

In a further embodiment, the multiple units are designed to comprise a core and a coating layer which comprises at least one thermoplastic excipient. This excipient is of pasty to semi-solid consistency at a temperature of about 20° C and has a melting point between about 25° C and about 100° C. In addition, the units comprise an outer membrane which is flexible and deformable, and which is based on an insoluble polymer providing extended release properties. Preferably, the multiple units of this embodiment represent pellets. The units are not only suitable for being filled into hard capsules; they may also be compressed into tablets.

In particular, the thermoplastic excipient is selected from partially hydrogenated oils, beeswax, carnauba wax, paraffin waxes, silicone waxes, fatty alcohols and fatty acids having 12 to 18 carbon atoms, solid, semi-synthetic glycerides, glycerol monoesters, diesters or triesters, polyoxyethylene glycols and glycosylated polyoxyethylenated glycerides, and mixtures thereof. Also, it is preferred that the outer membrane is well-plasticised, using at least one plasticiser such as triethyl citrate, acetyl triethyl citrate, tributyl citrate, acetyl tributyl citrate, triacetin, diethyl phthalate, polyethylene glycols, polysorbates, or mono- and diacetylated glycerides.

Another option is to design the multiple units as comprising a pramipexole-containing core formed from a hydrophilic material, a hydrophobic material or a hydrophobic emulsion or dispersion, and on the core an alternating sequence of hydrophilic and hydrophobic layers, such that there is a hydrophilic/hydrophobic interface between the core and each succeeding layer.

The multiple extended release units in the hard capsule can also be designed as individual extended release matrices. If this design is selected for the composition of the invention, it is preferred that the extended release units are selected from mini-tablets and pellets. Preferably, they are compressed mini-tablets. In this case, their formulation may follow the same principles and preferences that have been described herein-above in the context of extended release matrix tablets.

For example, the matrices may be formulated to comprise a glyceryl ester, preferably in amount of about 1 to 25 wt.-%, and a cellulose ether in amount of about 1 to 65 wt.-%. A particularly suitable glyceryl ester is glyceryl behenate, and the cellulose ether is preferably selected from hydroxypropyl methylcellulose, methylcellulose,

hydroxypropylcellulose, hydroxyethylcellulose, cellulose acetate, their derivatives and mixtures.

In another embodiment, multiple extended release matrix units comprise pramipexole dispersed in a mixture of least one hydrophobic long chain fatty acid, or ester thereof, and at least one surfactant. The content of the fatty acid derivative is at least 20 wt.-%, and that of the surfactant is at least 3 wt.-%, such as from about 3 to about 40 wt.-%. The hydrophobic fatty acid derivative is preferably glyceryl behenate, and the surfactant may be selected, for example, from polyglycolysed glycerides, polyoxyethylene sorbates, ethylene or propylene block copolymers and combinations of these. A particularly useful surfactant according to this embodiment is polyoxyethylene 20 sorbitan monolaurate.

According to a yet further embodiment, the composition may be designed as a hard capsule filled with one species of pellets which comprise both an immediate release dose fraction of substantially different from 0 % of the dose of pramipexole, and an extended release dose fraction. Such pellets may be designed to have two separate pramipexole-containing compartments and two separate polymeric excipient compartments, each of which envelops one of the active ingredient-containing compartments. For example, the pellet may comprise a core holding an extended release dose fraction of pramipexole, covered by a first polymeric compartment which controls the release of pramipexole from the core, which is in turn covered by a layer holding the immediate release dose fraction of pramipexole, which is covered by the second polymeric excipient layer. Using this principal design, various types of release rates can be accomplished, optionally using further features as described, for example, in US 5,885,616, which is incorporated herein by reference.

As a further option, the composition may comprise microparticles which provide extended release of pramipexole and which also exhibit bioadhesive properties by virtue of which the transit time of the multiple units through the upper gastrointestinal tract may potentially be prolonged. Such longer transit times may be advantageous because they could prevent that the particles are excreted before their incorporated dose of pramipexole has been released.

In particular, such particles may be designed as coated pramipexole dihydrochloride monohydrate particles which are coated with a coating composition comprising at least one film-forming polymer which is insoluble in gastric and intestinal fluids, at least one nitrogen-containing polymer selected from a polyacrylamide, a poly-N-vinylamide, a poly-N-vinyl-lactame, at least one plasticiser selected from glycerol esters, phthalates, citrates, sebacates, cetylalcohol esters, castor oil and cutin, and at least one surface-active and/or lubricating agent, selected from anionic and nonionic surfactants.

In this embodiment, the film-forming polymer which is insoluble in gastric and intestinal fluids is present at an amount of 50 to 90 wt.-% relative to the weight of the dry coating composition, and is preferably selected from ethylcellulose and cellulose acetate. The nitrogen-containing polymer is preferably a polyacrylamide and/or a polyvinylpyrrolidone, and present at a content of about 2 to 25 wt.-%, more preferably from about 5 to 15 wt.-%. Among the plasticisers, castor oil is particularly preferred; useful amounts range from about 2 to 20 wt.-%, or from 4 to 15 wt.-%. A useful content of the surfactant or lubricant also ranges from about 2 to 20 wt.-%, or from 4 to 15 wt.-%. Particularly useful excipients of this category include, for example, alkali metal or alkaline-earth metal salts of fatty acids, especially stearic acid and oleic acid, polyoxyethylene esters of sorbitan, polyoxyethylene derivatives of castor oil, stearylfumarates such as sodium stearylfimarate, and/or glyceryl behenate. The diameter of the coated particles is preferably between about 150 and 1,500 µm, especially from about 200 to about 800 µm.

One of the methods of making spherical pellets or microspheres which is useful in the practise of the invention is microspheronisation using flash heat and centrifugal forces. This method may be carried out, for example, by subjecting a liquefiable mixture of pramipexole and at least one excipient to flash heat by which the mixture is liquefied. Subsequently, shear force is applied to separate the mixture into discrete particles and to spheronise them. The critical step of rapidly liquefying the mixture and subjecting it to shear force is perhaps best conducted by spinning the mixture in a spinning head having a heated peripheral barrier with exit openings for passage of the liquefied in the presence of centrifugal force of spinning the head.

A preferred excipient which renders the mixture liquefiable is a sugar, such as sucrose. Further excipients may be incorporated in the mixture as needed. A particular advantage of this method is that it can rapidly and efficiently convert an active compound such as pramipexole into the form of microspheres which have highly suitable properties for subsequent film coating. For example, the method can be conducted to yield microsphere populations with defined sizes even well below 1 mm and with a narrow size distribution. Furthermore, the method can be conducted to yield particles with a highly spherical shape. Thus, the particles prepared by this method are suitable substrates onto which extended release coatings can be applied, as described herein-above. Without such extended release coatings, the pramipexole-containing particles may also be used as carriers for the immediate release dose fraction, if such fraction is different from 0 % of the pramipexole dose.

Further methods of making pellets, granules or microspheres which can be coated with an extended release coating include the agglomeration of powder mixtures comprising pramipexole in a high-shear mixer, fluid-bed agglomeration, powder layering in a pellet processor, or the extrusion of plasticised wet powders followed by spheronisation, preferably centrifugal spheronisation.

According to the extrusion method, spherically shaped pellets are produced by combining water, pramipexole and a suitable spheronising agent, such as microcrystalline cellulose, and further optional ingredients and extruding the wet mass through a small orifice, or assembly of orifices, of usually not more than about 2 mm. The water acts as a lubricant during this process and reduces the friction and heat generated during extrusion. Subsequently, the extruded material is placed into a spheroniser in which it is spun at high speeds. During this step the extrudates break and round into pellets, the size being determined by the size of the extrusion orifice. The extrudates need to be sufficiently moist to extrude, sufficiently dry to break and sufficiently moist to be spheronised, therefore the moisture content is one of the critical aspects of this method which must be optimised for each individual formulation according to common methods.

Instead of powder mixtures to be wetted for making an extrudable mass, the extrusion can also be performed as melt extrusion if a thermoformable carrier is used in

the formulation. Such carrier may be a wax or lipid, or more preferably a thermoplastic polymer, optionally plasticised with a suitable plasticiser.

Agglomeration of powders in high-shear mixers using granulation liquids or heat, depending on whether or not the formulation comprises a meltable binder, can be conducted under conditions by which relatively spheroidal, even though not typically spherical granules are obtained. In particular, a high input of mechanical energy is required. Instead of a high-shear mixer, a specialised apparatus with a rotating disc instead of an impeller may also be used.

Furthermore, nonpareils made of sucrose or other inert materials may be layered or coated with a pramipexole-containing powder in combination with a binder liquid. The process is preferably conducted in a specialised roto-processor.

As pointed out, the composition of the invention is useful for the prevention, diagnosis or treatment of Parkinson's disease or of a disease, symptom, or condition associated with, or resulting from, Parkinson's disease. The same is true for any medicinal products comprising the composition of the invention. Examples of forms of Parkinson's disease and associated symptoms and conditions include early, middle and late stage primary Parkinson's disease, secondary parkinsonism, postencephalitic parkinsonism, tremor, muscle rigidity, bradykinesia, hypokinesia, akinesia, muscular aches, fatigue, festination, propulsion, and retropulsion. Furthermore, the composition is potentially useful for the prevention, diagnosis or treatment of restless leg syndrome (RLS), fibromyalgia or any of the systems known under the name bipolar disorder(s) under conditions fall which include both maniac and depressive stages.

The use of the composition or of the medicinal product comprising the composition may for acute therapy, or sporadic. In one of the particularly preferred embodiments, the use involves regular administration over a period of at least one week, and preferably over a period of at least 2 weeks. In further embodiments, the regular administration is conducted at least over 4 weeks, or at least over 2 or 3 months, respectively.

The frequency of administration is preferably less than three times a day, such as twice a day or once a day. The composition of the invention is clearly suitable for twice daily administration, in particular for those patients who are sensitive to pramipexole or

to even moderate fluctuations of pramipexole plasma levels; such patients will benefit substantially from a twice daily dosing regimen of the composition as such regimen will lead to very smooth and even plasma levels. However, it is believed that for most patients, a tolerable, effective and convenient therapy is achieved with a once daily regimen, which is a feature of the presently most preferred use of the composition disclosed herein.

EXAMPLE 1

Nonpareil microcrystalline cellulose beads (986.4 g) were coated with a layering suspension comprising pramipexole dihydrochloride monohydrate (10.0 g), hydroxypropyl cellulose (2.0 g), talc (1.6 g), and purified water (400.0 g) and dried. From the resulting pramipexole-containing pellets, a portion (450.0 g) were film-coated with an extended release coating suspension comprising methacrylic acid copolymer type B (45.0 g), ammonio methacrylate copolymer type B (22.5 g), triacetin (11.0 g), talc (2.25 g), and ethanol 96% (1040 g) and dried. Pramipexol-containing pellets with and without extended release coating were mixed at various ratios: (a) 1 : 0; (b) 742.5 : 1.06; (c) 675 : 79.62; (d) 500 : 265.39. The mixtures were filled into hard capsules made of hydroxypropyl methyl cellulose in such amounts that each capsules comprised approx. 0.75 mg of pramipexole, calculated as pramipexole dihydrochloride monohydrate. The capsules comprised an immediate release dose fraction of 0 % (a), 1 % (b), 10 % (c), and 33.3 % (d), respectively, corresponding to an extended release fraction of 100 % (a), 99 % (b), 90 % (c), and 66.7 % (d) of the total incorporated pramipexole dose.

CLAIMS

1. Method for making a pharmaceutical extended release composition comprising a therapeutically effective dose of an active compound selected from pramipexole and its pharmaceutically acceptable salts, derivatives, solvates, and isomers, said method comprising the steps of:

(a) defining a desirable release profile;

(b) selecting a total dose of pramipexole to be incorporated in the composition;

(c) selecting a first fraction of said total dose to be incorporated in the composition in extended release form, and selecting a second fraction of said total dose to be incorporated in the composition in immediate release form; and

(d) combining said first and said second fractions into a composition exhibiting the release profile defined in step (a).

2. The method of claim 1, wherein the first fraction is in the range from about 50 to about 100 wt.-% and the second fraction is in the range from about 0 to about 50 wt.-%. of the total dose.

3. The method of claim 2, wherein the first fraction comprises about 100 wt.-% of the total dose.

4. The method of claim 1, wherein the first fraction comprises from about 0.375 to about 4.5 mg, and preferably from about 0.5 to about 1.5 mg of pramipexole, calculated as pramipexole dihydrochloride monohydrate.

5. The method of claim 1, wherein the active compound is pramipexole dihydrochloride monohydrate.

6. The method of claim 1, wherein the release profile selected in step (a) extends over a release period in the range from about 4 to about 24 hours, and preferably over at least 8 hours.

7. The method of claim 1, wherein the release profile selected in step (a) does not exhibit a lag phase of more than about 60 minutes, and preferably not more than about 30 minutes.

8. Pharmaceutical composition comprising a therapeutically effective dose of an active compound selected from pramipexole and its pharmaceutically acceptable salts, derivatives, solvates, and isomers, wherein a first fraction of said dose is incorporated in the composition in extended release form and a second fraction of the dose is incorporated in immediate release form.

9. The composition of claim 8, wherein the first fraction is in the range from about 50 to about 99.5 wt.-% and the second fraction is in the range from about 0.5 to about 50 wt.-%. of the total dose.

10. The composition of claim 9, wherein the first fraction is about 99.5 wt.-% of the total dose.

11. The composition of claim 8, wherein the first fraction exhibits a release profile having an initial lag phase, and wherein the composition exhibits a release profile having no initial lag phase.

12. The composition of claim 8, wherein the first fraction of the active compound is embedded in one or more matrices of at least one release-extending excipient selected from the group consisting of water-insoluble polymers, water-swellable polymers, lipids, and waxes.

13. The composition of claim 8, being formulated and processed as a single unit dosage form which is preferably a tablet, a hard capsule, a soft capsule, or an extrudate.

14. The composition of claim 8, being formulated and processed as a multiple unit dosage form which is preferably a tablet or a hard capsule.

15. The composition of claim 8, comprising one or more units, each unit comprising at least:

(a) a first compartment comprising the first fraction of the dose, and

(b) a second compartment which

- is spatially distinct from the first compartment,
- is substantially free of active compound, and
- comprises at least one release-extending excipient selected from the group consisting of water-insoluble polymers, water-swellable polymers, lipids, and waxes.

16. The composition of claim 15, wherein the second compartment covers the surface of the first compartment substantially completely.

17. The composition of claim 16, wherein the second compartment is a coating applied onto the first compartment by a film-coating or press-coating method.

18. The composition of claim 17, wherein the coating possesses at least one aperture having a diameter of less than about 1 mm^2, and more preferably of less than about 0.5 mm^2.

19. The composition of claim 8, wherein the first fraction comprises from about 0.375 to about 4.5 mg, and preferably from about 0.5 to about 1.5 mg of pramipexole, calculated as pramipexole dihydrochloride monohydrate.

20. The composition of claim 8, exhibiting a release profile which extends over a period in the range from about 4 to 24 hours and does not exhibit a lag phase of more than about 60 minutes, and preferably not more than about 30 minutes.